

## **DELIVERY OF PHYSIOLOGICALLY ACTIVE COMPOUNDS THROUGH AN INHALATION ROUTE**

**[0001]** This application is a continuation of U.S. patent application Ser. No. 10/154,765 entitled "Delivery of Physiologically Active Compounds Through an Inhalation Route," filed May 23, 2002, Rabinowitz and Zaffaroni, which priority to U.S. provisional application Serial No. 60/294,203 entitled "Thermal Vapor Delivery of Drugs," filed May 24, 2001, Rabinowitz and Zaffaroni and U.S. provisional application Serial No. 60/317,479 entitled "Aerosol Drug Delivery," filed September 5, 2001, Rabinowitz and Zaffaroni, the entire disclosures of which are hereby incorporated by reference.

### **Field of the Invention**

**[0002]** The present invention relates to the delivery of physiologically active compounds through an inhalation route. Specifically, it relates to aerosols containing physiologically active compounds that are used in inhalation therapy.

### **Background of the Invention**

**[0003]** It is desirable to provide a new route of administration for physiologically active compounds that rapidly produce peak plasma concentrations of the compound. The provision of such a route is an object of the present invention.

### **Summary of the Invention**

**[0004]** The present invention relates to the delivery of physiologically active compounds through an inhalation route. Specifically, it relates to aerosols containing physiologically active compounds that are used in inhalation therapy.

**[0005]** In a composition aspect of the present invention, the aerosol comprises particles comprising at least 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine. Preferably, the particles comprise at least 10 percent by weight of chlordiazepoxide, betahistine, clonidine,

testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent or 99.97 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine.

[0006] Typically, the aerosol has a mass of at least 1  $\mu\text{g}$ . Preferably, the aerosol has a mass of at least 10  $\mu\text{g}$ . More preferably, the aerosol has a mass of at least 20  $\mu\text{g}$ .

[0007] Typically, the aerosol particles comprise less than 10 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products. Preferably, the particles comprise less than 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products.

[0008] Typically, the aerosol particles comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent, 60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

[0009] Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

[0010] Typically, where the aerosol comprises chlordiazepoxide, the aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 40 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 30 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 3 mg/L and 20 mg/L.

[0011] Typically, where the aerosol comprises betahistine, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 50 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 30 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 20 mg/L.

[0012] Typically, where the aerosol comprises clonidine, the aerosol has an inhalable aerosol drug mass density of between 0.02 mg/L and 2 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.03 mg/L and 1.5 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 1 mg/L.

[0013] Typically, where the aerosol comprises testosterone, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 20 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 5 mg/L.

[0014] Typically, where the aerosol comprises conjugated estrogens or estrogen esters, the aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 5 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 2 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.15 mg/L and 1.5 mg/L.

[0015] Typically, where the aerosol comprises conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters, the aerosol has an inhalable aerosol drug mass density of between 0.001 mg/L and 0.2 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.002 mg/L and 0.1 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.004 mg/L and 0.05 mg/L.

[0016] Typically, where the aerosol comprises hyoscyamine, the aerosol has an inhalable aerosol drug mass density of between 0.01 mg/L and 1 mg/L. Preferably, the aerosol has an inhalable aerosol drug mass density of between 0.025 mg/L and 0.75 mg/L. More preferably, the aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 0.5 mg/L.

[0017] Typically, the aerosol has an inhalable aerosol particle density greater than  $10^6$  particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than

$10^7$  particles/mL. More preferably, the aerosol has an inhalable aerosol particle density greater than  $10^8$  particles/mL.

[0018] Typically, the aerosol particles have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

[0019] Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.85. More preferably, the geometric standard deviation is less than 2.7.

[0020] Typically, the aerosol is formed by heating a composition containing chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine to form a vapor and subsequently allowing the vapor to condense into an aerosol.

[0021] In a method aspect of the present invention, chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine is delivered to a mammal through an inhalation route. The method comprises: a) heating a composition, wherein the composition comprises at least 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine; and, b) allowing the vapor to cool, thereby forming a condensation aerosol comprising particles, which is inhaled by the mammal. Preferably, the composition that is heated comprises at least 10 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine. More preferably, the composition comprises 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine.

[0022] Typically, the delivered aerosol particles comprise at least 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or

hyoscyamine. Preferably, the particles comprise at least 10 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine. More preferably, the particles comprise at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine.

**[0023]** Typically, the delivered aerosol has a mass of at least 1  $\mu\text{g}$ . Preferably, the aerosol has a mass of at least 10  $\mu\text{g}$ . More preferably, the aerosol has a mass of at least 20  $\mu\text{g}$ .

**[0024]** Typically, the delivered aerosol particles comprise less than 10 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products. Preferably, the particles comprise less than 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products. More preferably, the particles comprise less than 2.5, 1, 0.5, 0.1 or 0.03 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products.

**[0025]** Typically, the particles of the delivered condensation aerosol have a mass median aerodynamic diameter of less than 5 microns. Preferably, the particles have a mass median aerodynamic diameter of less than 3 microns. More preferably, the particles have a mass median aerodynamic diameter of less than 2 or 1 micron(s).

**[0026]** Typically, the geometric standard deviation around the mass median aerodynamic diameter of the aerosol particles is less than 3.0. Preferably, the geometric standard deviation is less than 2.85. More preferably, the geometric standard deviation is less than 2.7.

**[0027]** Typically, the particles of the delivered condensation aerosol comprise less than 90 percent by weight of water. Preferably, the particles comprise less than 80 percent by weight of water. More preferably, the particles comprise less than 70 percent,

60 percent, 50 percent, 40 percent, 30 percent, 20 percent, 10 percent, or 5 percent by weight of water.

**[0028]** Typically, at least 50 percent by weight of the aerosol is amorphous in form, wherein crystalline forms make up less than 50 percent by weight of the total aerosol weight, regardless of the nature of individual particles. Preferably, at least 75 percent by weight of the aerosol is amorphous in form. More preferably, at least 90 percent by weight of the aerosol is amorphous in form.

**[0029]** Typically, where the aerosol comprises chlordiazepoxide, the delivered aerosol has an inhalable aerosol drug mass density of between 1 mg/L and 40 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 30 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 3 mg/L and 20 mg/L.

**[0030]** Typically, where the aerosol comprises betahistine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 50 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 2 mg/L and 30 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 5 mg/L and 20 mg/L.

**[0031]** Typically, where the delivered aerosol comprises clonidine, the aerosol has an inhalable aerosol drug mass density of between 0.02 mg/L and 2 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.03 mg/L and 1.5 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 1 mg/L.

**[0032]** Typically, where the aerosol comprises testosterone, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 20 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.2 mg/L and 10 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.5 mg/L and 5 mg/L.

**[0033]** Typically, where the aerosol comprises conjugated estrogens or estrogen esters, the delivered aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 5 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.1 mg/L and 2 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.15 mg/L and 1.5 mg/L.

[0034] Typically, where the aerosol comprises conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters, the delivered aerosol has an inhalable aerosol drug mass density of between 0.001 mg/L and 0.2 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.002 mg/L and 0.1 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.004 mg/L and 0.05 mg/L.

[0035] Typically, where the aerosol comprises hyoscyamine, the delivered aerosol has an inhalable aerosol drug mass density of between 0.01 mg/L and 1 mg/L. Preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.025 mg/L and 0.75 mg/L. More preferably, the delivered aerosol has an inhalable aerosol drug mass density of between 0.05 mg/L and 0.5 mg/L.

[0036] Typically, the delivered aerosol has an inhalable aerosol particle density greater than  $10^6$  particles/mL. Preferably, the aerosol has an inhalable aerosol particle density greater than  $10^7$  particles/mL. More preferably, the aerosol has an inhalable aerosol particle density greater than  $10^8$  particles/mL.

[0037] Typically, the rate of inhalable aerosol particle formation of the delivered condensation aerosol is greater than  $10^8$  particles per second. Preferably, the aerosol is formed at a rate greater than  $10^9$  inhalable particles per second. More preferably, the aerosol is formed at a rate greater than  $10^{10}$  inhalable particles per second.

[0038] Typically, the delivered aerosol is formed at a rate greater than 0.25 mg/second. Preferably, the aerosol is formed at a rate greater than 0.5 mg/second. More preferably, the aerosol is formed at a rate greater than 1 or 2 mg/second.

[0039] Typically, where the aerosol comprises chlordiazepoxide, between 1 mg and 40 mg of chlordiazepoxide is delivered to the mammal in a single inspiration. Preferably, between 2 mg and 30 mg of chlordiazepoxide is delivered to the mammal in a single inspiration. More preferably, between 3 mg and 20 mg of chlordiazepoxide is delivered to the mammal in a single inspiration.

[0040] Typically, where the aerosol comprises betahistine, between 0.5 mg and 50 mg of betahistine is delivered to the mammal in a single inspiration. Preferably, between 2 mg and 30 mg of betahistine is delivered to the mammal in a single inspiration. More preferably, between 5 mg and 20 mg of betahistine is delivered to the mammal in a single inspiration.

[0041] Typically, where the aerosol comprises clonidine, between 0.02 mg and 2 mg of clonidine is delivered to the mammal in a single inspiration. Preferably, between 0.03 mg and 1.5 mg of clonidine is delivered to the mammal in a single inspiration. More preferably, between 0.05 mg and 1 mg of clonidine is delivered to the mammal in a single inspiration.

[0042] Typically, where the aerosol comprises testosterone, between 0.1 mg and 20 mg of testosterone is delivered to the mammal in a single inspiration. Preferably, between 0.2 mg and 10 mg of testosterone is delivered to the mammal in a single inspiration. More preferably, between 0.5 mg and 5 mg of testosterone is delivered to the mammal in a single inspiration.

[0043] Typically, where the aerosol comprises conjugated estrogens or estrogen esters, between 0.05 mg and 5 mg of conjugated estrogens or estrogen esters is delivered to the mammal in a single inspiration. Preferably, between 0.1 mg and 2 mg of conjugated estrogens or estrogen esters is delivered to the mammal in a single inspiration. More preferably, between 0.15 mg and 1.5 mg of conjugated estrogens or estrogen esters is delivered to the mammal in a single inspiration.

[0044] Typically, where the aerosol comprises conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters, between 0.001 mg and 0.2 mg of conjugated conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters is delivered to the mammal in a single inspiration. Preferably, between 0.002 mg and 0.1 mg of conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters is delivered to the mammal in a single inspiration. More preferably, between 0.004 mg and 0.05 mg of conjugated estradiol, estradiol esters, ethinyl estradiol, or ethinyl estradiol esters is delivered to the mammal in a single inspiration.

[0045] Typically, where the aerosol comprises hyoscyamine, between 0.01 mg and 1 mg of hyoscyamine is delivered to the mammal in a single inspiration. Preferably, between 0.025 mg and 0.75 mg of hyoscyamine is delivered to the mammal in a single inspiration. More preferably, between 0.05 mg and 0.5 mg of hyoscyamine is delivered to the mammal in a single inspiration.

[0046] Typically, the delivered condensation aerosol results in a peak plasma concentration of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine in the mammal in less than 1 h. Preferably, the peak plasma

concentration is reached in less than 0.5 h. More preferably, the peak plasma concentration is reached in less than 0.2, 0.1, 0.05, 0.02, 0.01, or 0.005 h (arterial measurement).

[0047] In a kit aspect of the present invention, a kit for delivering chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine through an inhalation route to a mammal is provided which comprises: a) a composition comprising at least 5 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine; and, b) a device that forms a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol from the composition, for inhalation by the mammal. Preferably, the composition comprises at least 10 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine. More preferably, the composition comprises at least 20 percent, 30 percent, 40 percent, 50 percent, 60 percent, 70 percent, 80 percent, 90 percent, 95 percent, 97 percent, 99 percent, 99.5 percent, 99.9 percent or 99.97 percent by weight of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine.

[0048] Typically, the device contained in the kit comprises: a) an element for heating the chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine composition to form a vapor; b) an element allowing the vapor to cool to form an aerosol; and, c) an element permitting the mammal to inhale the aerosol.

#### Brief Description of the Figure

[0049] Fig. 1 shows a device used to deliver chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosols to a mammal through an inhalation route.

## Detailed Description of the Invention

### *Definitions*

[0050] “Aerodynamic diameter” of a given particle refers to the diameter of a spherical droplet with a density of 1 g/mL (the density of water) that has the same settling velocity as the given particle.

[0051] “Aerosol” refers to a suspension of solid or liquid particles in a gas.

[0052] “Aerosol drug mass density” refers to the mass of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine per unit volume of aerosol.

[0053] “Aerosol mass density” refers to the mass of particulate matter per unit volume of aerosol.

[0054] “Aerosol particle density” refers to the number of particles per unit volume of aerosol.

[0055] “Amorphous particle” refers to a particle that does not contain more than 50 percent by weight of a crystalline form. Preferably, the particle does not contain more than 25 percent by weight of a crystalline form. More preferably, the particle does not contain more than 10 percent by weight of a crystalline form.

[0056] “Betahistine” refers to N-methyl-2-pyridineethanamine.

[0057] “Betahistine degradation product” refers to a compound resulting from a chemical modification of betahistine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0058] “Chlordiazepoxide” refers to 7-chloro-N-methyl-5-phenyl-3H-1,4-benzodiazepin-2-amine 4-oxide.

[0059] “Chlordiazepoxide degradation product” refers to a compound resulting from a chemical modification of chlordiazepoxide. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0060] “Clonidine” refers to 2,6-dichloro-N-2-imidazolidinylidene-benzeneamine.

[0061] “Clonidine degradation product” refers to a compound resulting from a chemical modification of clonidine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0062] “Condensation aerosol” refers to an aerosol formed by vaporization of a substance followed by condensation of the substance into an aerosol.

[0063] “Conjugated estrogen” refers to estrogen sulfates. This includes a blend of estrogen sulfates containing estrone, equilin, and 17  $\alpha$ -dihydroequilin.

[0064] “Conjugated estrogen degradation product” refers to a compound resulting from a chemical modification of a conjugated estrogen. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0065] “Estradiol” refers to estra-1,3,5(10)-triene-3,17-diol.

[0066] “Estradiol degradation product” refers to a compound resulting from a chemical modification of estradiol. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0067] “Estradiol ester” refers to an ester derived from the esterification of an alcohol moiety of estradiol.

[0068] “Estradiol ester degradation product” refers to a compound resulting from a chemical modification of an estradiol ester. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0069] “Estrogen ester” refers to an ester derived from the esterification of an alcohol moiety of estrogen.

[0070] “Estrogen ester degradation product” refers to a compound resulting from a chemical modification of an estrogen ester. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0071] “Ethinyl estradiol” refers to 19-nor-17 $\alpha$ -pregna-1,3,5(10)-trien-20-yne-3,17-diol.

[0072] “Ethinyl estradiol degradation product” refers to a compound resulting from a chemical modification of ethinyl estradiol. The modification, for example, can be the

result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0073] “Ethinyl estradiol ester” refers to an ester derived from the esterification of an alcohol moiety of ethinyl estradiol.

[0074] “Ethinyl estradiol ester degradation product” refers to a compound resulting from a chemical modification of an ethinyl estradiol ester. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0075] “Hyoscyamine” refers to  $\alpha$ -(hydroxymethyl)benzeneacetic acid 8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester.

[0076] “Hyoscyamine degradation product” refers to a compound resulting from a chemical modification of hyoscyamine. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0077] “Inhalable aerosol drug mass density” refers to the aerosol drug mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0078] “Inhalable aerosol mass density” refers to the aerosol mass density produced by an inhalation device and delivered into a typical patient tidal volume.

[0079] “Inhalable aerosol particle density” refers to the aerosol particle density of particles of size between 100 nm and 5 microns produced by an inhalation device and delivered into a typical patient tidal volume.

[0080] “Mass median aerodynamic diameter” or “MMAD” of an aerosol refers to the aerodynamic diameter for which half the particulate mass of the aerosol is contributed by particles with an aerodynamic diameter larger than the MMAD and half by particles with an aerodynamic diameter smaller than the MMAD.

[0081] “Rate of aerosol formation” refers to the mass of aerosolized particulate matter produced by an inhalation device per unit time.

[0082] “Rate of inhalable aerosol particle formation” refers to the number of particles of size between 100 nm and 5 microns produced by an inhalation device per unit time.

[0083] “Rate of drug aerosol formation” refers to the mass of aerosolized chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine produced by an inhalation device per unit time.

[0084] “Settling velocity” refers to the terminal velocity of an aerosol particle undergoing gravitational settling in air.

[0085] “Testosterone” refers to 17 $\beta$ -hydroxyandrost-4-en-3-one.

[0086] “Testosterone degradation product” refers to a compound resulting from a chemical modification of testosterone. The modification, for example, can be the result of a thermally or photochemically induced reaction. Such reactions include, without limitation, oxidation and hydrolysis.

[0087] “Typical patient tidal volume” refers to 1 L for an adult patient and 15 mL/kg for a pediatric patient.

[0088] “Vapor” refers to a gas, and “vapor phase” refers to a gas phase. The term “thermal vapor” refers to a vapor phase, aerosol, or mixture of aerosol-vapor phases, formed preferably by heating.

***Formation of Physiologically Active Compound Containing Aerosols***

[0089] Any suitable method is used to form the aerosols of the present invention. A preferred method, however, involves heating a composition comprising chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine to form a vapor, followed by cooling of the vapor such that it condenses to provide an chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine comprising aerosol (condensation aerosol). The composition is heated in one of four forms: as pure active compound (*i.e.*, pure chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine) as a mixture of active compound and a pharmaceutically acceptable excipient; as a salt form of the pure active compound; and, as a mixture of active compound salt form and a pharmaceutically acceptable excipient.

[0090] Salt forms of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine are either commercially available or are obtained from the corresponding free base using well known methods in the art. A variety of pharmaceutically acceptable salts are suitable for aerosolization. Such salts include,

without limitation, the following: hydrochloric acid, hydrobromic acid, acetic acid, maleic acid, formic acid, and fumaric acid salts.

**[0091]** Pharmaceutically acceptable excipients may be volatile or nonvolatile. Volatile excipients, when heated, are concurrently volatilized, aerosolized and inhaled with the antihistamine. Classes of such excipients are known in the art and include, without limitation, gaseous, supercritical fluid, liquid and solid solvents. The following is a list of exemplary carriers within the classes: water; terpenes, such as menthol; alcohols, such as ethanol, propylene glycol, glycerol and other similar alcohols; dimethylformamide; dimethylacetamide; wax; supercritical carbon dioxide; dry ice; and mixtures thereof.

**[0092]** Solid supports on which the composition is heated are of a variety of shapes. Examples of such shapes include, without limitation, cylinders of less than 1.0 mm in diameter, boxes of less than 1.0 mm thickness and virtually any shape permeated by small (*e.g.*, less than 1.0 mm-sized) pores. Preferably, solid supports provide a large surface to volume ratio (*e.g.*, greater than 100 per meter) and a large surface to mass ratio (*e.g.*, greater than 1 cm<sup>2</sup> per gram).

**[0093]** A solid support of one shape can also be transformed into another shape with different properties. For example, a flat sheet of 0.25 mm thickness has a surface to volume ratio of approximately 8,000 per meter. Rolling the sheet into a hollow cylinder of 1 cm diameter produces a support that retains the high surface to mass ratio of the original sheet but has a lower surface to volume ratio (about 400 per meter).

**[0094]** A number of different materials are used to construct the solid supports. Classes of such materials include, without limitation, metals, inorganic materials, carbonaceous materials and polymers. The following are examples of the material classes: aluminum, silver, gold, stainless steel, copper and tungsten; silica, glass, silicon and alumina; graphite, porous carbons, carbon yarns and carbon felts; polytetrafluoroethylene and polyethylene glycol. Combinations of materials and coated variants of materials are used as well.

**[0095]** Where aluminum is used as a solid support, aluminum foil is a suitable material. Examples of silica, alumina and silicon based materials include amorphous silica S-5631 (Sigma, St. Louis, MO), BCR171 (an alumina of defined surface area greater than 2 m<sup>2</sup>/g from Aldrich, St. Louis, MO) and a silicon wafer as used in the semiconductor industry. Carbon yarns and felts are available from American Kynol, Inc.,

New York, NY. Chromatography resins such as octadecyl silane chemically bonded to porous silica are exemplary coated variants of silica.

[0096] The heating of the chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine compositions is performed using any suitable method. Examples of methods by which heat can be generated include the following: passage of current through an electrical resistance element; absorption of electromagnetic radiation, such as microwave or laser light; and, exothermic chemical reactions, such as exothermic solvation, hydration of pyrophoric materials and oxidation of combustible materials.

***Delivery of Physiologically Active Compound Containing Aerosols***

[0097] Chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosols of the present invention are delivered to a mammal using an inhalation device. Where the aerosol is a condensation aerosol, the device has at least three elements: an element for heating a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing composition to form a vapor; an element allowing the vapor to cool, thereby providing a condensation aerosol; and, an element permitting the mammal to inhale the aerosol. Various suitable heating methods are described above. The element that allows cooling is, in its simplest form, an inert passageway linking the heating means to the inhalation means. The element permitting inhalation is an aerosol exit portal that forms a connection between the cooling element and the mammal's respiratory system.

[0098] One device used to deliver a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol is described in reference to Fig. 1. Delivery device 100 has a proximal end 102 and a distal end 104, a heating module 106, a power source 108, and a mouthpiece 110. A chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine composition is deposited on a surface 112 of heating module 106. Upon activation of a user activated switch 114, power source 108 initiates heating of heating module 106 (e.g, through

ignition of combustible fuel or passage of current through a resistive heating element). The chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine composition volatilizes due to the heating of heating module 106 and condenses to form a condensation aerosol prior to reaching the mouthpiece 110 at the proximal end of the device 102. Air flow traveling from the device distal end 104 to the mouthpiece 110 carries the condensation aerosol to the mouthpiece 110, where it is inhaled by the mammal.

**[0099]** Devices, if desired, contain a variety of components to facilitate the delivery of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosols. For instance, the device may include any component known in the art to control the timing of drug aerosolization relative to inhalation (e.g., breath-actuation), to provide feedback to patients on the rate and/or volume of inhalation, to prevent excessive use (i.e., “lock-out” feature), to prevent use by unauthorized individuals, and/or to record dosing histories.

***Dosage of Physiologically Active Compound Containing Aerosols***

**[00100]** The dosage amount of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine in aerosol form is generally no greater than twice the standard dose of the drug given orally. The following dosage amounts are typical for the respective compounds: chlordiazepoxide, 10 mg; betahistine, 16 mg; clonidine, 0.1 mg; testosterone, 5 mg; conjugated estrogens and estrogen esters, 0.625 mg; estradiol, estradiol esters, ethinyl estradiol and ethinyl estradiol esters, 0.02 mg; and, hyoscyamine, 0.15 mg. As aerosols, doses are generally provided as follows for the same indications: chlordiazepoxide, 1 to 40 mg; betahistine, 0.5 to 50 mg; clonidine, 0.02 to 2 mg; testosterone, 0.1 to 20 mg; conjugated estrogens and estrogen esters, 0.05 to 5 mg; estradiol, estradiol esters, ethinyl estradiol and ethinyl estradiol esters, 0.001 mg to 0.2 mg; and, hyoscyamine, 0.01 to 1 mg. A typical dosage of a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine aerosol is either administered as a single inhalation or as a series of inhalations taken within an hour or less (dosage equals

sum of inhaled amounts). Where the drug is administered as a series of inhalations, a different amount may be delivered in each inhalation.

**[0100]** One can determine the appropriate dose of a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol to treat a particular condition using methods such as animal experiments and a dose-finding (Phase I/II) clinical trial. One animal experiment involves measuring plasma concentrations of drug in an animal after its exposure to the aerosol. Mammals such as dogs or primates are typically used in such studies, since their respiratory systems are similar to that of a human. Initial dose levels for testing in humans is generally less than or equal to the dose in the mammal model that resulted in plasma drug levels associated with a therapeutic effect in humans. Dose escalation in humans is then performed, until either an optimal therapeutic response is obtained or a dose-limiting toxicity is encountered.

#### *Analysis of Physiologically Active Compound Containing Aerosols*

**[0101]** Purity of a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol is determined using a number of methods, examples of which are described in Sekine *et al.*, *Journal of Forensic Science* 32:1271-1280 (1987) and Martin *et al.*, *Journal of Analytic Toxicology* 13:158-162 (1989). One method involves forming the aerosol in a device through which a gas flow (e.g., air flow) is maintained, generally at a rate between 0.4 and 60 L/min. The gas flow carries the aerosol into one or more traps. After isolation from the trap, the aerosol is subjected to an analytical technique, such as gas or liquid chromatography, that permits a determination of composition purity.

**[0102]** A variety of different traps are used for aerosol collection. The following list contains examples of such traps: filters; glass wool; impingers; solvent traps, such as dry ice-cooled ethanol, methanol, acetone and dichloromethane traps at various pH values; syringes that sample the aerosol; empty, low-pressure (e.g., vacuum) containers into which the aerosol is drawn; and, empty containers that fully surround and enclose the aerosol generating device. Where a solid such as glass wool is used, it is typically extracted with a solvent such as ethanol. The solvent extract is subjected to analysis

rather than the solid (*i.e.*, glass wool) itself. Where a syringe or container is used, the container is similarly extracted with a solvent.

**[0103]** The gas or liquid chromatograph discussed above contains a detection system (*i.e.*, detector). Such detection systems are well known in the art and include, for example, flame ionization, photon absorption and mass spectrometry detectors. An advantage of a mass spectrometry detector is that it can be used to determine the structure of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine degradation products.

**[0104]** Particle size distribution of a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol is determined using any suitable method in the art (*e.g.*, cascade impaction). An Andersen Eight Stage Non-viable Cascade Impactor (Andersen Instruments, Smyrna, GA) linked to a furnace tube by a mock throat (USP throat, Andersen Instruments, Smyrna, GA) is one system used for cascade impaction studies.

**[0105]** Inhalable aerosol mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the mass collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient.

**[0106]** Inhalable aerosol drug mass density is determined, for example, by delivering a drug-containing aerosol into a confined chamber via an inhalation device and measuring the amount of active drug compound collected in the chamber. Typically, the aerosol is drawn into the chamber by having a pressure gradient between the device and the chamber, wherein the chamber is at lower pressure than the device. The volume of the chamber should approximate the tidal volume of an inhaling patient. The amount of active drug compound collected in the chamber is determined by extracting the chamber, conducting chromatographic analysis of the extract and comparing the results of the chromatographic analysis to those of a standard containing known amounts of drug.

**[0107]** Inhalable aerosol particle density is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device and measuring the

number of particles of given size collected in the chamber. The number of particles of a given size may be directly measured based on the light-scattering properties of the particles. Alternatively, the number of particles of a given size may be determined by measuring the mass of particles within the given size range and calculating the number of particles based on the mass as follows: Total number of particles = Sum (from size range 1 to size range N) of number of particles in each size range. Number of particles in a given size range = Mass in the size range/Mass of a typical particle in the size range. Mass of a typical particle in a given size range =  $\pi * D^3 * \phi / 6$ , where D is a typical particle diameter in the size range (generally, the mean boundary MMADs defining the size range) in microns,  $\phi$  is the particle density (in g/mL) and mass is given in units of picograms ( $g^{-12}$ ).

**[0108]** Rate of inhalable aerosol particle formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (e.g., 3 s), and the number of particles of a given size collected in the chamber is determined as outlined above. The rate of particle formation is equal to the number of 100 nm to 5 micron particles collected divided by the duration of the collection time.

**[0109]** Rate of aerosol formation is determined, for example, by delivering aerosol phase drug into a confined chamber via an inhalation device. The delivery is for a set period of time (e.g., 3 s), and the mass of particulate matter collected is determined by weighing the confined chamber before and after the delivery of the particulate matter. The rate of aerosol formation is equal to the increase in mass in the chamber divided by the duration of the collection time. Alternatively, where a change in mass of the delivery device or component thereof can only occur through release of the aerosol phase particulate matter, the mass of particulate matter may be equated with the mass lost from the device or component during the delivery of the aerosol. In this case, the rate of aerosol formation is equal to the decrease in mass of the device or component during the delivery event divided by the duration of the delivery event.

**[0110]** Rate of drug aerosol formation is determined, for example, by delivering a chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol into a confined chamber via an inhalation device over a set period of time (e.g., 3 s). Where the aerosol is pure chlordiazepoxide, betahistine, clonidine,

testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine, the amount of drug collected in the chamber is measured as described above. The rate of drug aerosol formation is equal to the amount of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine collected in the chamber divided by the duration of the collection time. Where the chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine containing aerosol comprises a pharmaceutically acceptable excipient, multiplying the rate of aerosol formation by the percentage of chlordiazepoxide, betahistine, clonidine, testosterone, conjugated estrogens, estrogen esters, estradiol, estradiol esters, ethinyl estradiol, ethinyl estradiol esters, or hyoscyamine in the aerosol provides the rate of drug aerosol formation.

***Utility of Physiologically Active Compound Containing Aerosols***

[0111] Chlordiazepoxide containing aerosols are typically used for the treatment of anxiety. Betahistine containing aerosols are typically used for the treatment of vertigo (Meniere's disease). Clonidine containing aerosols are typically used for the treatment of alcohol withdrawal, nicotine withdrawal, sedation, or hot flashes. Testosterone containing aerosols are typically used for testosterone replacement therapy. Conjugated estrogens and estrogen ester containing aerosols are typically used for hormone replacement therapy (menopause). Estradiol, estradiol ester, ethinyl estradiol, and ethinyl estradiol ester containing aerosols are typically used for hormone replacement therapy (estradiol and esters) and the prevention of pregnancy (ethinyl estradiol and esters). Hyoscyamine containing aerosols are typically used for the treatment of peptic ulcers.

[0112] The following examples are meant to illustrate, rather than limit, the present invention.

[0113] Chlordiazepoxide hydrochloride, betahistine dihydrochloride, clonidine hydrochloride, testosterone, estradiol, certain estradiol esters, and hyoscyamine are commercially available from Sigma ([www.sigma-aldrich.com](http://www.sigma-aldrich.com)). Obtaining a free base from a salt or esterifying an alcohol are done according to standard methods in the art.

Compounds such as ethinyl estradiol are isolated from commercially available pharmaceutical preparations or synthesized using standard methods in the art.

### EXAMPLE 1

#### *General Procedure for Volatilizing Compounds*

[0114] A solution of drug in approximately 120  $\mu$ L dichloromethane is coated on a 3 cm x 8 cm piece of aluminum foil. The dichloromethane is allowed to evaporate. The coated foil is wrapped around a 300 watt halogen tube (Feit Electric Company, Pico Rivera, CA), which is inserted into a glass tube sealed at one end with a rubber stopper. Running 60 V (45 V for chlordiazepoxide) of alternating current (driven by line power controlled by a variac) through the bulb for 5 to 15 s affords thermal vapor (including aerosol), which is collected on the glass tube walls. Reverse-phase HPLC analysis with detection by absorption of 225 nm light is used to determine the purity of the aerosol. (When desired, the system is flushed through with argon prior to volatilization.)

[0115] The following aerosol purities were obtained using this method: chlordiazepoxide (99% purity, 1.3 mg); estradiol-17-acetate (98.6% purity, 0.59 mg); estradiol-3,17-diacetate (96.9% purity, 1.07 mg); testosterone (100% purity, 0.93 mg); and, hyoscyamine (95.9% purity, 1.07 mg).

[0116] To obtain higher purity aerosols, one can coat a lesser amount of drug, yielding a thinner film to heat. A linear decrease in film thickness is associated with a linear decrease in impurities.